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The long-term outcome of interstitial lung disease with anti-aminoacyl-tRNA synthetase antibodies

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ABSTRACT

Rationale: Anti-aminoacyl transfer RNA synthetase antibodies (anti-ARS) are a group of myositis-specific autoantibodies that are detected in the sera of patients with polymyositis and dermatomyositis (PM/DM) and also in those of patients with idiopathic interstitial pneumonias without any connective tissue disease (CTD), including PM/DM. Although we reported the clinical characteristics of interstitial lung disease with anti-ARS antibodies (ARS-ILD) with and without PM/DM, the long-term prognosis of ARS-ILD remains undetermined. As our previous studies revealed that ARS-ILD without PM/DM was similar to CTD-associated ILD, and that ARS-ILD with PM/DM was radiologically suggestive of a nonspecific interstitial pneumonia (NSIP) pathological pattern, we hypothesized that the prognosis of ARS-ILD might be distinct from that of idiopathic pulmonary fibrosis (IPF) without anti-ARS.

Objectives: To elucidate the long-term outcome of ARS-ILD with and without PM/DM and compare it to that of IPF.

Methods: A two-center retrospective study was conducted. The study population comprised 36 patients with ARS-ILD (8 with PM, 12 with DM, and 16 without myositis throughout the course), 100 patients with IPF without anti-ARS, and 7 patients with NSIP without anti-ARS. The presence of anti-ARS was determined by RNA immunoprecipitation using the sera obtained at the time of diagnosis before specific treatment.

Measurements and main results: During the observational period (median 49 months; range, 1–114 months), 7 patients with ARS-ILD (19%; 3 with PM, 1 with DM, and 3 without PM/DM) and 51 patients with IPF (51%) died. Patients with ARS-ILD had better overall survival than those with IPF (log-rank test, $P < 0.001$) and similar survival compared to those with NSIP (log-rank test, $P = 0.59$). The prognosis for patients with ARS-ILD was similar between those with and without myositis (log-rank test, $P = 0.91$). At the median follow-up time of 76.5 months, 14 of the 36 patients with ARS-ILD had deteriorated. Both a decline in forced vital capacity or an initiation of long-term oxygen therapy during the course (odds ratio [OR], 5.34) and acute exacerbation (OR, 28.4) significantly increased the mortality risk.

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Conclusions: The long-term outcome of ARS-ILD was significantly better than that of IPF regardless of the presence or absence of myositis.

Abbreviations

AE	acute exacerbation
AFILD	autoimmune-featured interstitial lung disease
anti-ARS	anti-aminoacyl transfer RNA synthetase antibodies
ARS-ILD	interstitial lung disease with anti-ARS antibodies
ATS	American Thoracic Society
CK	creatine kinase
CS	corticosteroid
CTD	connective tissue disease
DM	dermatomyositis
ERS	European Respiratory Society
FVC	forced vital capacity
HR	hazard ratio
HRCT	high-resolution computed tomography
IPAF	interstitial pneumonia with autoimmune features
IPF	idiopathic pulmonary fibrosis
IS	immunosuppressive agent
KL-6	Krebs von der Lungen-6
LD-CTD	lung dominant-connective tissue disease
LDH	lactate dehydrogenase
LTOT	long-term oxygen therapy
MSAs	myositis-specific autoantibodies
NSIP	nonspecific interstitial pneumonia
OR	odds ratio
PFTs	pulmonary function tests
PM	polymyositis
RA	rheumatoid arthritis
SP-D	surfactant protein-D
UCTD	undifferentiated connective tissue disease
UIP	usual interstitial pneumonia
$\%FEV_1$	the percentage to predicted forced expiratory volume in 1 s
%FVC	the percentage to predicted forced vital capacity
95% CI	95% confidence interval

1. Introduction

Anti-aminoacyl transfer RNA synthetase antibodies (anti-ARS) are a group of myositis-specific autoantibodies (MSAs) associated with polymyositis and dermatomyositis (PM/DM)-associated interstitial lung disease (ILD) and with idiopathic interstitial pneumonias (IIPs) without any connective tissue disease (CTD); [1,2]. We previously reported that anti-ARS-associated ILD (ARS-ILD) without PM/DM was similar to idiopathic nonspecific interstitial pneumonia (NSIP) and to CTD-associated interstitial lung disease (CTD-ILD) with regard to the radiological and pathological features at presentation [2]. ARS-ILD with PM/DM was also radiologically and pathologically similar to idiopathic NSIP [3,4]. Those findings led to the hypothesis that the prognosis of ARS-ILD without PM/DM should be better than that of idiopathic pulmonary fibrosis (IPF) and similar to that of ARS-ILD with PM/DM.

Several previous studies addressed the clinical spectrum associated with anti-ARS as an antisythetase syndrome. A recent meta-analysis included 3478 patients with anti-ARS from 27 studies and revealed different manifestations in patients that were positive and negative, respectively, for anti-Jo-1 [5]. On the other hand, most of the previous studies were restricted to patients with PM/DM, and the long-term outcome of ARS-ILD without idiopathic inflammatory myositis has not been elucidated. When focused on ILD, the prognosis of ARS-ILD should be compared to those of chronic IIPs without anti-ARS, and particularly that of IPF, because IPF is representative of the major IIPs [6,7]. In addition, the impacts of myositis on survival should be examined within the whole spectrum of ARS-ILD.

This retrospective study was conducted to investigate the long-term outcomes of ARS-ILD with and without PM/DM. We compared the prognosis between patients with ARS-ILD and those with IPF and also examined the prognostic factors for patients with ARS-ILD. Through these analyses, we sought to place ARS-ILD within the context of IIPs and CTD-ILD.

2. Material and methods

2.1. Study subjects

The patient enrollment process is outlined in Fig. 1. Serum anti-ARS were screened in 237 consecutive patients who were newly diagnosed with IIPs at Kyoto University Hospital between June 2007 and April 2011 and at Tenri Hospital, a tertiary care center, between January 2005 and April 2011. Eighteen patients were positive for anti-ARS (ARS-ILD without myositis). Among the remaining 219 patients with IIPs without anti-ARS, 101 and 8 had IPF and NSIP, respectively. IIPs were diagnosed and classified according to the 2002 American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [8]. One patient with IPF and one with NSIP developed rheumatoid arthritis (RA) after the initial diagnosis and were excluded from the analysis.

To enroll patients with ARS-ILD with myositis, anti-ARS were assessed in 51 consecutive patients who were newly diagnosed with PM/DM-ILD at Kyoto University Hospital between July 2007 and April 2011 and at Tenri Hospital between January 2005 and April 2009. Twenty of those patients were positive for anti-ARS (8 with PM and 12 with DM). Two patients with ARS-ILD without myositis at the time of diagnosis later developed PM/DM and were reclassified as having ARS-ILD with myositis. PM and DM were diagnosed using Bohan and Peter's criteria [9], and ILD was diagnosed by high-resolution computed tomography (HRCT). Additionally, clinically amyopathic dermatomyositis (C-ADM) was diagnosed if a patient had the characteristic skin rash of DM with little or no muscle symptoms and a serum creatine kinase (CK) level <300 IU/L at the time of diagnosis [4,10,11].

Thus, the study population comprised 16 patients with ARS-ILD without myositis, 20 patients with ARS-ILD with myositis, 100 patients with anti-ARS-negative IPF, and 7 patients with anti-ARS-negative NSIP. Of those, 11 patients with ARS-ILD without myositis, 20 patients with ARS-ILD with myositis, 52 patients with

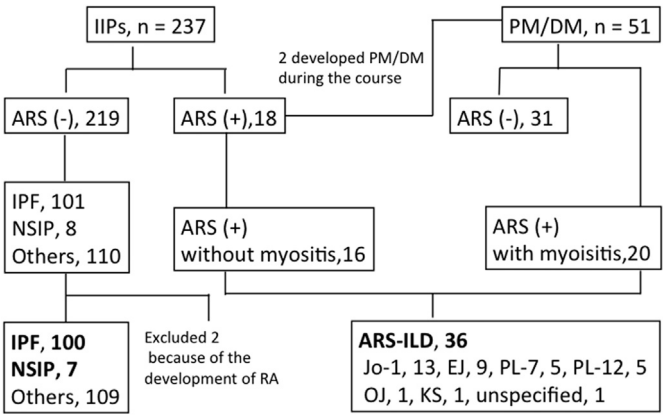

Fig. 1. Flow chart of patient enrollment.

anti-ARS-negative IPF, and 4 patients with anti-ARS-negative NSIP had been included in our previous study [2,4].

Patients were excluded if they had an active neoplasm or other CTD at the time of diagnosis or had been treated with systemic corticosteroid (CS) or an immunosuppressive agent (IS) before referral to our hospitals. Written informed consent was obtained from the participants, and the Ethics Committee of Kyoto University Hospital and that of Tenri Hospital approved the study (E2119 and No. 635, respectively).

2.2. Clinical evaluation

Clinical information was retrospectively collected from medical records. All patients with ARS-ILD were evaluated by at least two rheumatologists prior to treatment. The patients had blood tests at their first visit and underwent standardized pulmonary function tests (PFTs) [12]. Published equations were used to determine the predicted values for each parameter [13].

For patients with ARS-ILD, chest HRCT images prior to treatment were reviewed by two of three potential independent observers (T.K., T.H., and K.T. with 20, 17, and 15 years of experience, respectively) who were blinded to the patients' clinical information. Interobserver disagreements were resolved by consensus. Images were assessed according to the recommendations of the Nomenclature Committee of the Fleischner Society for the presence of ground-glass attenuation, consolidation, intralobular reticular opacities, interlobular septal thickening, nonseptal linear or plate-like opacity, substantial micronodules, honeycombing, traction bronchiectasis, and lobar volume loss [14]. Nonseptal linear or plate-like opacity was defined as an elongated line of soft-tissue attenuation that was distinct from interlobular septa and bronchovascular bundles, including subpleural curvilinear lines and subpleural bands [4].

2.3. Measurement of MSAs

Serum samples were obtained from all patients at the first visit prior to any specific therapies including anti-fibrotic drugs, CS, and IS. The presence of anti-ARS (anti-Jo-1, anti-PL7, anti-EJ, anti-OJ, anti-PL12, and anti-KS) was determined by RNA-immunoprecipitation as previously described [2,10].

2.4. Long-term outcomes

The primary long-term outcome was overall survival. When a patient underwent lung transplantation, the case was censored at the time of transplantation. Episodes of acute exacerbation (AE) were collected from medical records. AE was diagnosed as follows: unexplained worsening or development of dyspnea within the previous 30 days; new diffuse pulmonary infiltrates on chest radiography or high-resolution computed tomography since the preceding visit; and exclusion of any known causes of acute worsening including infection, left heart failure, pulmonary embolism, and any identifiable cause of acute lung injury in accordance with routine clinical practice and microbiologic studies [15,16].

In patients with ARS-ILD, the response to initial treatment and chronic progression were also assessed. Initial improvement was defined as 10% or more improvement in forced vital capacity (FVC) after the initial treatment. PFT results were assessed at the point nearest to 6 months after the treatment was started. Chronic progression was defined as: (1) 10% or more decline in FVC at the latest measurement from baseline and/or (2) the development of chronic respiratory failure requiring long-term oxygen therapy (LTOT).

2.5. Statistical analyses

Statistical analyses were performed using JMP® version 9.0 (SAS Institute Inc. Cary, NC, USA). All statistical variations in quantitative data were expressed as a single-determination standard deviation, and $P < 0.05$ was considered statistically significant.

Group comparisons were made using Fisher's exact tests, Mann-Whitney U tests, or Wilcoxon's tests. Survival curves were drawn using the Kaplan-Meier method and compared using log-rank tests. Survival analysis was performed to define the prognostic factors for patients with ARS-ILD. The Cox proportional hazards model was used for univariate analysis; multivariate analysis was not performed, because few patients with ARS-ILD died.

3. Results

3.1. Clinical features

The study participants' characteristics are summarized in Table 1. Compared with patients with IPF, those with ARS-ILD were younger (53.9 ± 10.2 years vs. 67.9 ± 6.8 years, $P < 0.01$) and included fewer males (36.1% vs. 78.0%, $P < 0.01$) and fewer current or former smokers (47.2% vs. 79.0%, $P < 0.01$). Serum lactate dehydrogenase (LDH) levels were significantly higher in patients with ARS-ILD than in those with IPF (380 ± 217 IU/L vs. 234 ± 50 IU/L, $P < 0.01$), whereas serum surfactant protein-D (SP-D) levels, the percentage to predicted FVC (%FVC), and the percentage to predicted forced expiratory volume in 1 s (%FEV_1) were significantly lower in patients with ARS-ILD (SP-D, 199 ± 241 ng/mL vs. 227 ± 171 ng/mL, $P < 0.01$; %FVC 73.8 ± 20.7% vs. 83.1 ± 20.8%, $P = 0.04$; %FEV_1 71.2 ± 18.0% vs. 84.1 ± 18.1%, $P < 0.01$). Pathological diagnoses were available for 46 patients (none with ARS-ILD with myositis, 10 with ARS-ILD without myositis, 29 with IPF, and 7 with NSIP). The pathological patterns of the patients with ARS-ILD were NSIP in seven patients (70%) and usual interstitial pneumonia (UIP) in three patients (30%). Pirfenidone and LTOT were used less commonly to treat patients with ARS-ILD than to treat patients with IPF (pirfenidone, 0.0% vs. 26.0%, $P < 0.01$; LTOT, 11.1% vs. 41.0%, $P < 0.01$), while more patients with ARS-ILD were treated with CS and IS (CS, 91.7% vs. 44.0%, $P < 0.01$; IS, 75.0% vs. 32.0%, $P < 0.01$).

The characteristics of the patients with ARS-ILD with and without myositis are shown in Table 2. Of the 36 patients with ARS-ILD, 8 had PM, 12 had DM (including 4 with C-ADM), and 16 did not develop myositis. Of the 20 patients with ARS-ILD with myositis, 9 were positive for anti-Jo-1, 4 were positive for anti-PL7, 3 were positive for anti-EJ, 2 were positive for anti-OJ, 1 was positive for

Table 1
Patient characteristics.

	ARS-ILD (n = 36)	IPF (n = 100)	NSIP (n = 7)
Age, years	53.9 ± 10.2*†	67.9 ± 6.8	62.3 ± 6.3‡
Male	13 (36.1%)*	78 (78.0%)	4 (58%)
Smoking	17 (47.2%)*	79 (79.0%)	4 (57%)
mMRC, [1–5]	1.9 ± 1.1	1.9 ± 1.0	1.4 ± 0.5
LDH, IU/L	380 ± 217*†	234 ± 50	248 ± 99
KL-6, U/mL	1244 ± 952	1215 ± 967	1546 ± 1536
SP-D, ng/mL	199 ± 241*	227 ± 171	165 ± 129
PaO_2, Torr	81.5 ± 14.6	80.9 ± 12.2	95.3 ± 28.9
%FVC	73.8 ± 20.7*	83.1 ± 20.8	69.9 ± 18.3
$\%FEV_1$	71.2 ± 18.0*	84.1 ± 18.1	76.1 ± 9.0
%DLCO	55.3 ± 13.7	51.1 ± 18.7	52.2 ± 16.0
Treatment			
Pirfenidone	0 (0.0%)*	26 (26.0%)	0 (0.0%)
Corticosteroid	33 (91.7%)*	44 (44.0%)	6 (85.7%)‡
Immunosuppressive agent	27 (75.0%)*	32 (32.0%)	4 (57.1%)
LTOT	4 (11.1%)*	41 (41.0%)	2 (28.6%)
Follow-up time, months	72.4 ± 22.7*	46.8 ± 28.7	90.3 ± 38.9
Mortality/transplantation	7 (19.4%)*	54 (54.0%)	3 (42.9%)

Data are presented as mean ± standard deviation (SD) or n (%). Numbers in square brackets represent the theoretical score range.
*$P < 0.05$ vs. IPF, †$P < 0.05$ vs. NSIP, ‡$P < 0.05$ vs. IPF.
Abbreviations: ARS-ILD, interstitial lung disease with anti-aminoacyl transfer RNA synthetase antibodies; %DLCO, percentage of predicted diffusion capacity of carbon monoxide; $\%FEV_1$, percentage of predicted forced expiratory volume in 1 s; %FVC, percentage of predicted forced vital capacity; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von der Lungen-6; LDH, lactate dehydrogenase; LTOT, long-term oxygen therapy; mMRC, modified Medical Research Council; NSIP, nonspecific interstitial pneumonia; PaO_2, partial pressure of oxygen; SP-D, surfactant protein-D.

anti-PL12, and 1 was positive for an unspecified anti-ARS. Of the 16 patients with ARS-ILD without myositis, 6 were positive for anti-EJ, 4 were positive for anti-Jo-1, 4 were positive for anti-PL12, 1 was positive for anti-PL7, and 1 was positive for anti-OJ. The prevalence of anti-Jo-1 positivity was similar between patients with and without myositis (30.0% with myositis vs. 25.0% without myositis, $P = 0.19$). The anti-ARS were mutually exclusive in all patients with ARS-ILD. Serum LDH, creatine kinase (CK), and aldolase levels were significantly higher in patients with myositis (LDH, 473 ± 249 IU/L with myositis vs. 263 ± 70 IU/L without myositis, $P < 0.01$; CK, 2022 ± 3066 IU/L vs. 113 ± 108 IU/L, $P < 0.01$; aldolase, 31.9 ± 38.5 ng/mL vs. 6.1 ± 3.2 ng/mL, $P < 0.01$), while serum Krebs von der Lungen-6 (KL-6) was marginally lower in those with myositis (942 ± 607 U/mL vs. 1650 ± 1182 U/mL, $P = 0.08$). PFTs and treatment were similar between the two groups.

Table 2
ARS-ILD patient characteristics.

	With myositis (n = 20)	Without myositis (n = 16)	*P* value
Age, years	51.7 ± 11.6	56.7 ± 7.4	0.09
Male	5 (25.0%)	8 (50.0%)	NS
Smoking	8 (40.0%)	9 (56.3%)	NS
mMRC, [1–5]	2.0 ± 1.1	1.7 ± 1.1	NS
MSA profile			
Jo-1	9 (45.0%)	4 (25.0%)	NS
PL-7	4 (20.0%)	1 (6.3%)	NS
EJ	3 (15.0%)	6 (37.5%)	NS
PL-12	1 (5.0%)	4 (25.0%)	NS
LDH, IU/L	473 ± 249	263 ± 70	<0.01
CK, IU/L	2022 ± 3066	113 ± 108	<0.01
Aldolase, ng/mL	31.9 ± 38.5	6.1 ± 3.2	<0.01
KL-6, U/mL	942 ± 607	1650 ± 1182	0.08
SP-D, ng/mL	113 ± 85	305 ± 357	NS
PaO_2, Torr	78.8 ± 17.8	84.4 ± 9.9	NS
%FVC	75.6 ± 18.2	71.9 ± 23.4	NS
$\%FEV_1$	73.7 ± 14.9	68.5 ± 21.0	NS
%DLCO	54.8 ± 10.1	55.9 ± 17.5	NS
Treatment			
Pirfenidone	0 (0.0%)	0 (0.0%)	NS
Corticosteroid	20 (100.0%)	13 (81.3%)	0.08
Immunosuppressive agent	16 (80.0%)	11 (68.8%)	NS
LTOT	3 (15.0%)	1 (6.3%)	NS
Follow-up time, months	77.6 ± 22.0	66.0 ± 22.5	NS
Mortality	4 (20.0%)	3 (18.8%)	NS

Data are presented as mean ± standard deviation (SD) or number (%). Numbers in square brackets represent a theoretical score range.
Abbreviations: ARS-ILD, interstitial lung disease with anti-aminoacyl transfer RNA synthetase antibodies; CK, creatine kinase; %DLCO, percentage of predicted diffusion capacity of carbon monoxide; $\%FEV_1$, percentage of forced expiratory volume in 1 s; %FVC, percentage of predicted forced vital capacity; KL-6, Krebs von der Lungen-6; LDH, lactate dehydrogenase; LTOT, long-term oxygen therapy; mMRC, modified Medical Research Council; PaO_2, partial pressure of oxygen; SP-D, surfactant protein-D.

3.2. Overall survival

The overall survival is shown in Fig. 2 and Table 3. The overall survival of patients with ARS-ILD was significantly better than that of patients with anti-ARS-negative IPF (log-rank, $P < 0.001$, Fig. 2A) and similar to that of patients with anti-ARS-negative NSIP (log-rank, $P = 0.59$, Fig. 2A). Among the patients with ARS-ILD, the overall survival was similar between those with and without myositis (log-rank, $P = 0.90$, Fig. 2B). At the median follow-up time of 80 months (range, 36–114), four (20%) patients with ARS-ILD with myositis had died (three of AE and one of pneumonia). At the median follow-up time of 72 months (range, 21–94), three (19%) patients with ARS-ILD without myositis had died (two of an AE and one of pneumonia).

3.3. Long-term outcomes of ARS-ILD

The initial treatment for ARS-ILD and the patients' responses are listed in Table 4. At the median follow-up time of 76.5 months, 14 of 36 (38.9%) patients with ARS-ILD had eventually deteriorated: 10% or more decline in FVC in 9 patients (25.0%), AE in 9 patients (25.0%), death due to respiratory causes in 7 patients (19.4%), and chronic respiratory failure requiring LTOT in 4 patients (11.1%).

Patients with ARS-ILD with and without chronic progression throughout their courses were similar at the time of diagnosis, although the scale of mMRC, the level of serum SP-D, and the frequency of ground-glass opacities were marginally higher in those with chronic progression (Table S1).

3.4. Prognostic factors for overall mortality in ARS-ILD

The univariate regression analyses of overall mortality are shown in Table 5. Among several clinical parameters, chronic progression and AE conferred significant risks of mortality (chronic progression: hazard ratio [HR] = 5.34, 95% confidence interval [95% CI] = 1.15–37.4, $P = 0.03$; AE: HR = 28.4, 95% CI = 4.65–547.5, $P < 0.01$). Dyspnea, serum biomarkers, and PFTs at the time of diagnosis or initial improvement were not associated with mortality.

4. Discussion

This retrospective study demonstrated that the prognosis of ARS-ILD was significantly better than that of anti-ARS-negative IPF and was similar between patients with and without myositis. Chronic disease progression and AE were predictors of mortality in patients with ARS-ILD.

Our results suggest that ARS-ILD is similar to CTD-ILD rather than to IPF in terms of long-term outcomes, even when no sign of myositis is observed. The prognosis of CTD-ILD is better than those of IIPs and IPF [17], and the predominance of a pathological NSIP pattern is considered a major reason for better survival [18–20].

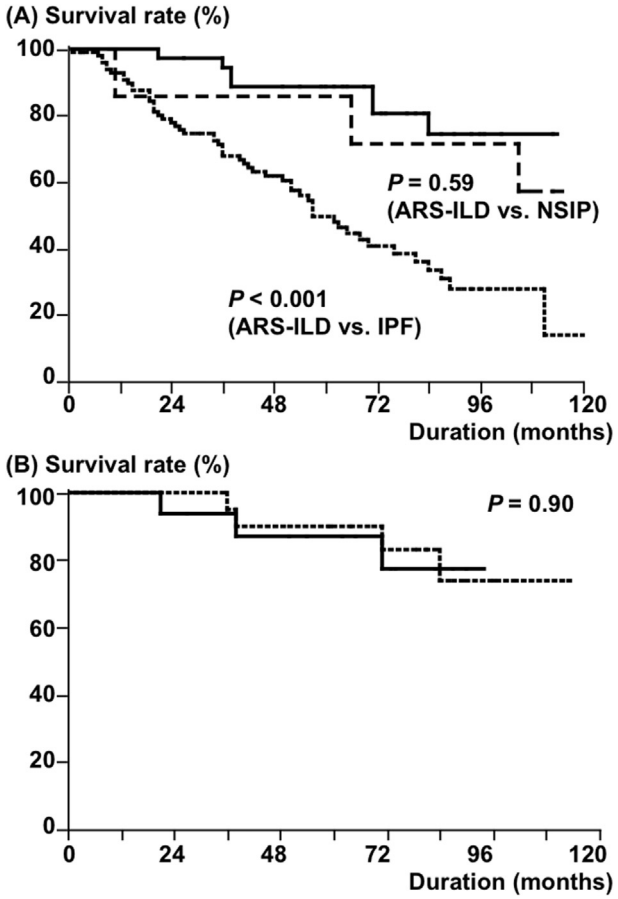

Fig. 2. (A) Kaplan-Meier curves comparing the survival rates of patients with interstitial lung disease with anti-aminoacyl transfer RNA synthetase antibodies (ARS-ILD, solid line), nonspecific interstitial pneumonia (NSIP, dashed line), and idiopathic pulmonary fibrosis (IPF, dotted line).
Abbreviations: ARS-ILD, interstitial lung disease with anti-aminoacyl transfer RNA synthetase antibodies; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia.
(B) Kaplan-Meier curves comparing the survival rates of ARS-ILD patients with (dotted line) and without myositis (solid line).

Indeed, a pathological NSIP pattern confers a better prognosis than a pathological UIP pattern in CTD-ILD and RA-associated ILD [17,20,21]. Our previous and current studies indicate that the most common pathological pattern of ARS-ILD is NSIP, and radiological findings are also consistent with an NSIP pattern [2,4,11]. Hozumi et al. also reported a similar predominance of pathological and radiological NSIP patterns in ARS-ILD, although their study was restricted to patients with DM/PM-ILD [3]. In addition, the long-term survival of patients with ARS-ILD (including those with and without myositis) in our cohort was comparable to that of the patients with idiopathic NSIP (anti-ARS-negative) in our cohort and also to that reported in an ATS project [22]. Collectively, these findings suggest that the pathological predominance of NSIP may confer a better prognosis in ARS-ILD, although not all patients with ARS-ILD have this pattern.

Table 4
Responses to the initial treatment of ARS-ILD.

Initial treatment (n = 36)	
Corticosteroid monotherapy	14 (38.9%)
Corticosteroid and immunosuppressive agent	19 (52.8%)
None	3 (8.3%)
Follow-up assessment after the initial treatment (n = 17)	
Duration, months	9.1 ± 5.7
Initial improvement	13 (76.5%)
Corticosteroid monotherapy (n = 5)	4 (80.0%)
Corticosteroid and immunosuppressive agent (n = 12)	9 (75.0%)

Data are presented as the mean ± standard deviation (SD) or number (%).
Abbreviation: ARS-ILD, interstitial lung disease with anti-aminoacyl transfer RNA synthetase antibodies.

Table 5
Univariate analyses of overall mortality in ARS-ILD.

	Hazard ratio	95% CI	*P* value
Age	1.07	0.99–1.15	0.07
Male	1.38	0.27–6.28	NS
Smoking	1.43	0.32–7.26	NS
mMRC	1.05	0.45–1.97	NS
Myositis	0.90	0.20–4.61	NS
LDH, 10IU/L	1.00	0.95–1.03	NS
KL-6, 100U/mL	1.04	0.96–1.10	NS
SP-D, 10 ng/mL	1.02	1.00–1.03	NS
%FVC	0.99	0.95–1.03	NS
$\%FEV_1$	0.99	0.94–1.04	NS
%DLCO	0.95	0.87–1.02	NS
Chronic progression	5.34	1.15–37.4	0.03
Initial improvement	0.32	0.17–1.98	NS
Chronic respiratory failure	3.54	0.50–16.6	NS
Acute exacerbations	28.4	4.65–547.5	<0.01

AbbreviationsARS-ILD, interstitial lung disease with anti-aminoacyl transfer RNA synthetase antibodies; CI, confidence interval; %DLco, percentage of predicted diffusion capacity of carbon monoxide; %FEV1, percentage of forced expiratory volume in 1 s; %FVC, percentage of predicted forced vital capacity; KL-6, Krebs von der Lungen-6; LDH, lactate dehydrogenase; mMRC, modified Medical Research Council; SP-D, surfactant protein-D.

Table 3
Overall transplantation-free survival.

	ARS-ILD (n = 36)	IPF (n = 100)	NSIP (n = 7)
Follow-up period, months	76.5 (21–114)	46.5 (1–121)	76.5 (11–116)
Death	7 (19.4%)	53 (53.0%)	2 (29.0%)
Transplantation	0 (0.0%)	1 (1.0%)	0 (0.0%)
Cause of death			
Acute exacerbation	5 (71.4%)	18 (34.0%)	2 (100.0%)
Pneumonia	2 (28.6%)	3 (5.7%)	0 (0.0%)
Chronic respiratory failure	0 (0.0%)	18 (34.0%)	0 (0.0%)
Lung cancer	0 (0.0%)	4 (7.5%)	0 (0.0%)
Sudden death	0 (0.0%)	4 (7.5%)	0 (0.0%)
Pneumothorax	0 (0.0%)	3 (5.7%)	0 (0.0%)
Extrapulmonary causes	0 (0.0%)	4 (7.5%)	0 (0.0%)

Data are presented as median (range) or n (%).
Abbreviations: ARS-ILD, interstitial lung disease with anti-aminoacyl transfer RNA synthetase antibodies; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia.

This study also revealed that patients with ARS-ILD with and without myositis had similar survival. The favorable prognosis of patients with ARS-ILD with myositis has been previously reported. Hozumi et al. demonstrated that the 5-year and 10-year survival rates of patients with anti-ARS-positive PM/DM were 100% and 91.6–92.3%, respectively [3], and Yoshfuji et al. reported a 2-year survival rate of 95% [23]. We expanded those findings to the entire spectrum of ARS-ILD regardless of the presence or absence of myositis. Takato et al. reported that ARS-ILD had similar radiological and physiological features between patients with and without PM/DM, and the responses to the initial treatment were also comparable [24]. In another Japanese study, 27.0% of patients with ARS-ILD without myositis at presentation developed PM/DM during long-term observation [25]. Thus, the distinction between ARS-ILD with and without myositis may be provisional. These results and our survival analysis consistently indicate that ARS-ILD can be categorized into a single entity regardless of the presence or absence of myositis, at least in terms of ILD.

According to the current ATS/ERS classification, ARS-ILD without myositis is included among the IIPs when it does not fulfill the criteria for PM/DM or any other CTD [7,26]. On the other hand, autoimmune features such as Raynaud's phenomenon, autoantibodies, and lymphoid follicles have been reported in many patients with IIPs [7,27–29]. The presence of anti-ARS is also among those features [27]. Thus, several attempts have been made to categorize patients with IIPs who have autoimmune features but do not meet the criteria for a particular CTD: undifferentiated connective tissue disease (UCTD), lung dominant-connective tissue disease (LD-CTD), and autoimmune-featured interstitial lung disease (AFILD).

Recently, interstitial pneumonia with autoimmune features (IPAF) was added to those attempts [27]. The classification criteria for IPAF consist of the clinical, serological, and morphological domains, and the presence of anti-ARS is included in the serological domain. Given the morphological features of ARS-ILD, almost all cases of ARS-ILD without myositis can fulfill the criteria for IPAF. IPAF can cover a broader spectrum of IIPs than ARS-ILD, while ARS-ILD can also be categorized into a single entity regardless of the presence or absence of myositis.

Compared to IPAF and other similar entities, ARS-ILD had some notable characteristics in our study. First, both the clinical features at presentation and the long-term patient survival in ARS-ILD were different from those in IPF, as shown in our previous and current studies [2,4,11]. The different prognosis may reflect differences in pathology and response to treatment. These findings suggest that the detection of anti-ARS in the serum can readily categorize patients with IIPs whose clinical features are different from those of patients with IPF, in contrast to other classifications based on the collection of several CTD features. Another characteristic of ARS-ILD is that it is defined more specifically than the other proposed entities mentioned above. The clinical, radiological, and pathological features and outcomes of CTD-ILD are different among individual CTDs, particularly between RA and others [18–20,30]. ILD manifestations are also variable, even within a single CTD. PM/DM-ILD includes distinct subtypes that are strongly associated with outcomes and MSA profiles [4,10,11]. Additionally, multicomponent involvement of the respiratory system such as small-airway and pleural diseases is another characteristic of CTDs and may complicate individual cases of CTD-ILD. These features raise the concern that the composite criteria of clinical and serological autoimmune features may include elements of different CTDs that are too varied or nonspecific to identify a specific ILD category. Consequently, defined UTCD, LD-CTD, or AFILD may not be different enough from IPF in terms of long-term outcomes [30–33]. On the contrary, anti-ARS have been associated with a specific subtype of PM/DM-ILD [1,25], and our previous studies and current findings have expanded our knowledge of the specific role of anti-ARS in the context of IIPs [2].

Another main result of this study is that approximately 40% of patients with ARS-ILD experienced long-term deterioration, although the response to initial treatment was favorable in most cases. Chronic progression and AE were associated with mortality in patients with ARS-ILD, while the initial data at presentation, such as dyspnea, physiological impairment, serum biomarkers, and the response to initial treatment, could not predict long-term survival. These findings contrast with the clinical features of IPF. IPF is essentially refractory to both CS and IS, and the disease severity at presentation has been the main prognostic determinant, indicating that current therapies cannot sufficiently improve the natural course of IPF [6,29,34].

In contrast to their lack of efficacy in IPF, the current regimens consisting of CS or of CS and IS can alter the course of ARS-ILD, at least initially. On the other hand, such therapies may prove to be insufficient to prevent chronic progression or AE in some cases, which may eventually lead to a fatal outcome. Although the long-term survival of patients with ARS-ILD is better that of those with IPF, ARS-ILD can be a progressive and fatal disease even with long-term IS therapies. To improve the long-term survival of patients with ARS-ILD, novel therapies beyond CS and IS that can prevent refractory fibrosis progression and AE development are required.

This study has certain limitations. First, the impacts of a pathological UIP pattern on the long-term outcome of ARS-ILD could not be addressed, because pathological diagnoses were available for only a limited numbers of patients with ARS-ILD. Although an NSIP pattern is the most common pattern in ARS-ILD, some patients have a UIP pattern, which may affect the prognosis in those patients as well as in patients with RA-ILD [19–21,35]. Second, the clinical courses could not be compared among patients with different anti-ARS profiles. The clinical manifestations of PM/DM and ILD in patients with anti-ARS were recently compared according to stratification with individual anti-ARS, although they were relatively homogenous [25,36,37]. Third, the study participants did not receive uniform treatment. In particular, considering the results of the PANTHER-IPF study [38], CS/IS combination therapy may have affected the long-term outcome for patients with IPF in our study population.

Despite these limitations, our results have demonstrated that the long-term outcome of ARS-ILD was significantly better than that of IPF, indicating that ARS-ILD is an entity independent from IPF regardless of the presence of myositis. On the other hand, approximately 40% of patients with ARS-ILD suffered from progressive and refractory disease, and novel therapies beyond CS and IS are required.

Author's contributions

KT collected, analyzed, and interpreted the data and drafted the article. TH was fully responsible for data integrity and accuracy of data analysis; developing the concept and design of the study; collecting, analyzing, and interpreting the data; and critically revising the draft article. RN, TK, YH, KW, KA, KI, AS, YN, YT, KH, SN, YK, and AY collected, analyzed, and interpreted data and critically revised the draft article. TO and TH critically revised the draft article. KC, SN, TI, TM, and MM revised the draft article and approved final revisions.

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Author disclaimers

The views expressed in this article do not communicate an official position of the institutions or funding sources.

Competing interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2017.04.007.

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